CDER New Drug Review: 2015 Update

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Housekeeping

- Data and analyses presented on the following slides are thought to be accurate. In order to provide the most up-to-date information the analyses have not undergone the same thorough quality control as is performed for official FDA reports
- Many staff in CDER provided data, analyses, and PowerPoint expertise for this talk; their work behind the scenes makes me look good each year. Special thanks and acknowledgement to:
  - The Performance Analysis and Data Services Staff in CDER's Office of Program and Strategic Analysis
  - Mike Lanthier in the Office of the Commissioner
- Pay attention to fiscal year (FY) or calendar year (CY) and cut-off dates on data presentations

Themes in new drug review for 2015

- The PDUFA V NME Program is widely viewed as a success
  - Positive interim report issued by an independent contractor[1]
- Continued growth of breakthrough designations/approvals
  - Workshop held to help clarify FDA's decisions on designations[2]
- Continued interest in Priority Review Vouchers (PRVs)
  - GAO study of rare pediatric PRV program ongoing
- NME first-cycle approval rates at historically high levels
- US continues to lead the world in first approval of NMEs
- Continued growth of biosimilar program
- Despite successes, significant challenges remain
  - Increasing workload placing strain on program resources
  - Recruitment and retention of staff remains a major challenge

[1] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM436448.pdf

[2] http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria

Topics to be covered

- How is CDER doing with regard to meeting PDUFA goals?
- What are the trends in new drug approvals?
  - IND activity, NME submissions, and NME approvals
  - Utilization and impact of expedited programs
- Implementation of PDUFA V/FDASIA programs
  - "Program" for NME review
  - Breakthrough Therapy Designation Program

What about PDUFA Goals?

- FDA continues to meet or exceed nearly all PDUFA goals for application review
- We continue to implement new programs under PDUFA V and FDASIA as resources and competing priorities allow
  - Continued budget uncertainty due to CRs, shutdown threats, etc.
  - Some progress in improving staffing in OND
    - 916 FTEs on board at start of PDUFA V/FDASIA (FY13)
    - 1014 FTEs on board at start of FY16
    - Still below current authorized ceiling of 1067 FTEs
      - FTE ceiling does not adequately reflect staffing requirements to meet increasing workload and expectations; e.g., meetings, BT, biosimilars, PFDD, PRVs, stakeholder engagement, staff training and PD, guidance…….
  - Federal hiring system, HHS pay caps, outdated GS pay system, etc. continue to adversely impact our ability to recruit and retain the highly trained staff we need to do our important public health work

What About New Drug Approvals?

- The commercial IND pipeline remains strong
  - Growth driven mostly by biologics
- For CY15, through December 9th, 2015, CDER has:
  - Received 36 NME applications
  - Approved 41 NMEs*, including 19 Orphan Drugs
- First cycle approval rates are at historic highs
  - Median time to approval up slightly as expected due to NME Program filing review "off the clock"
- From start of BT program through November 30, 2015:
  - CDER has received 307 requests for BT designation
  - CDER has granted a 95 BT designations
  - Approved 20 BT original/supplemental applications

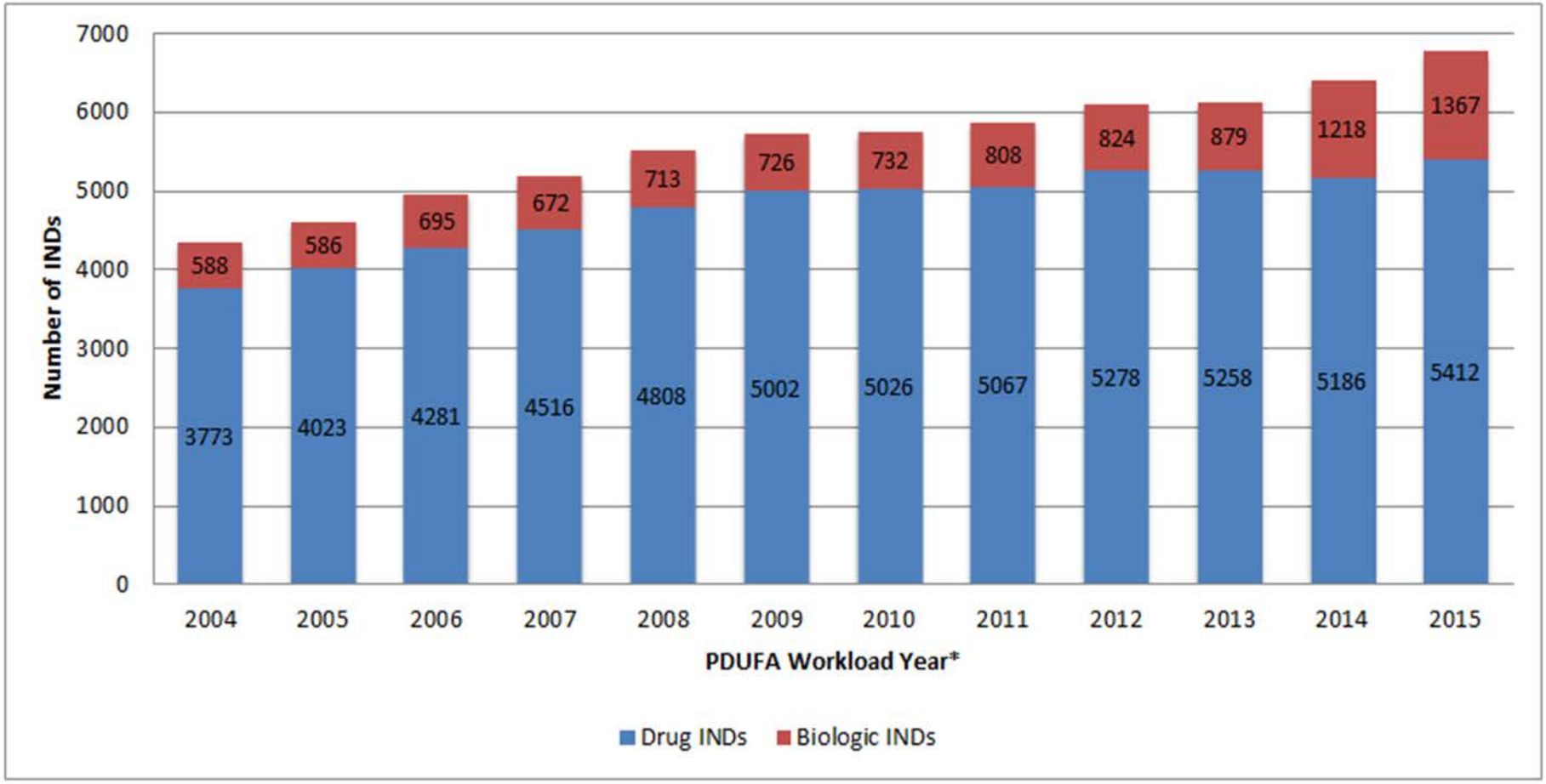
* This information is accurate as of December 9, 2015. In rare instances, it may be necessary for FDA to change a drug's new molecular entity (NME) designation or the status of its application as a novel new biologics license application (BLA). For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug's designation or the status of an application as a novel BLA, the Agency intends to communicate the nature of, and the reason for, any revisions as appropriate. This note applies to all references to NME/Original BLAs in this presentation.

CDER PDUFA V Review Performance

	FY 2014		FY 2015	
Submission Type	Number Filed	Performance (Current)	Number Filed	Performance (Potential)**
Priority NME NDAs/original BLAs	24	96%	25	100%
Standard NME NDAs/original BLAs	14	93%	19	100%
Priority non-NME NDAs/BLAs*	10	80%	8	100%
Standard non-NME NDAs/BLAs*	72	97%	69	99%
Class 1 NDA/BLA Resubmissions	6	100%	6	100%
Class 2 NDA/BLA Resubmissions	32	97%	35	100%
Priority Efficacy Supplements	40	100%	37	98%
Standard Efficacy Supplements	146	90%	94	100%
Class 1 Efficacy Resubmissions	7	100%	0	--
Class 2 Efficacy Resubmissions	8	88%	7	100%
Prior Approval Mfg Supplements	542	93%	455	94%
CBE Mfg Supplements	1017	95%	1017	97%

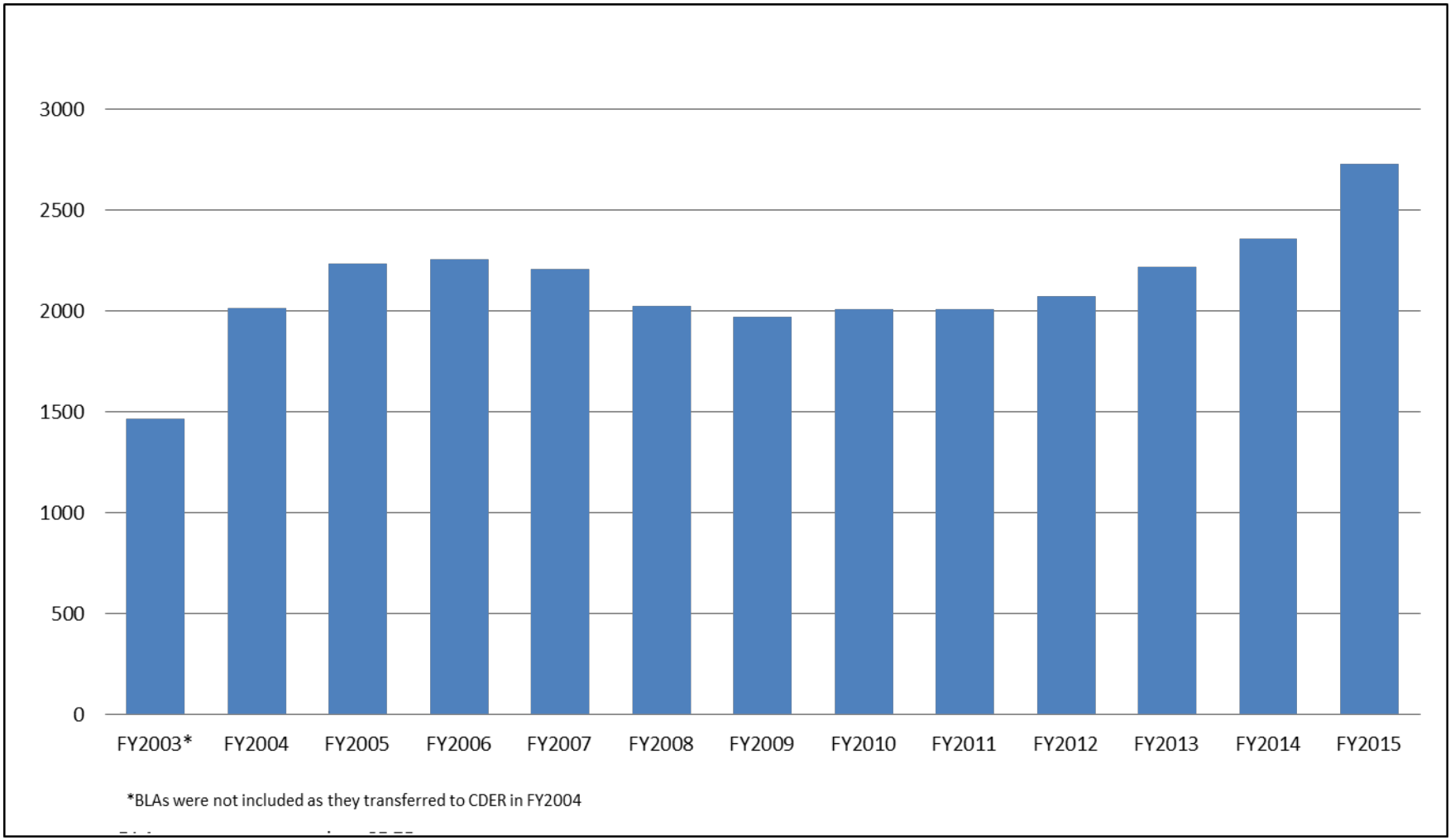
Data as of 9/30/2015
*Beginning in FY 2013, the new tracked metrics are non-NME Priority and non-NME Standard NDAs.
† Includes submissions pending filing.
**Potential Performance refers to the level of performance that could potentially be achieved if all the actions currently pending are reviewed within their required goal date. Submissions with unknown review schedules are excluded.

Commercial INDs With Activity Based On PDUFA Workload Adjuster Data



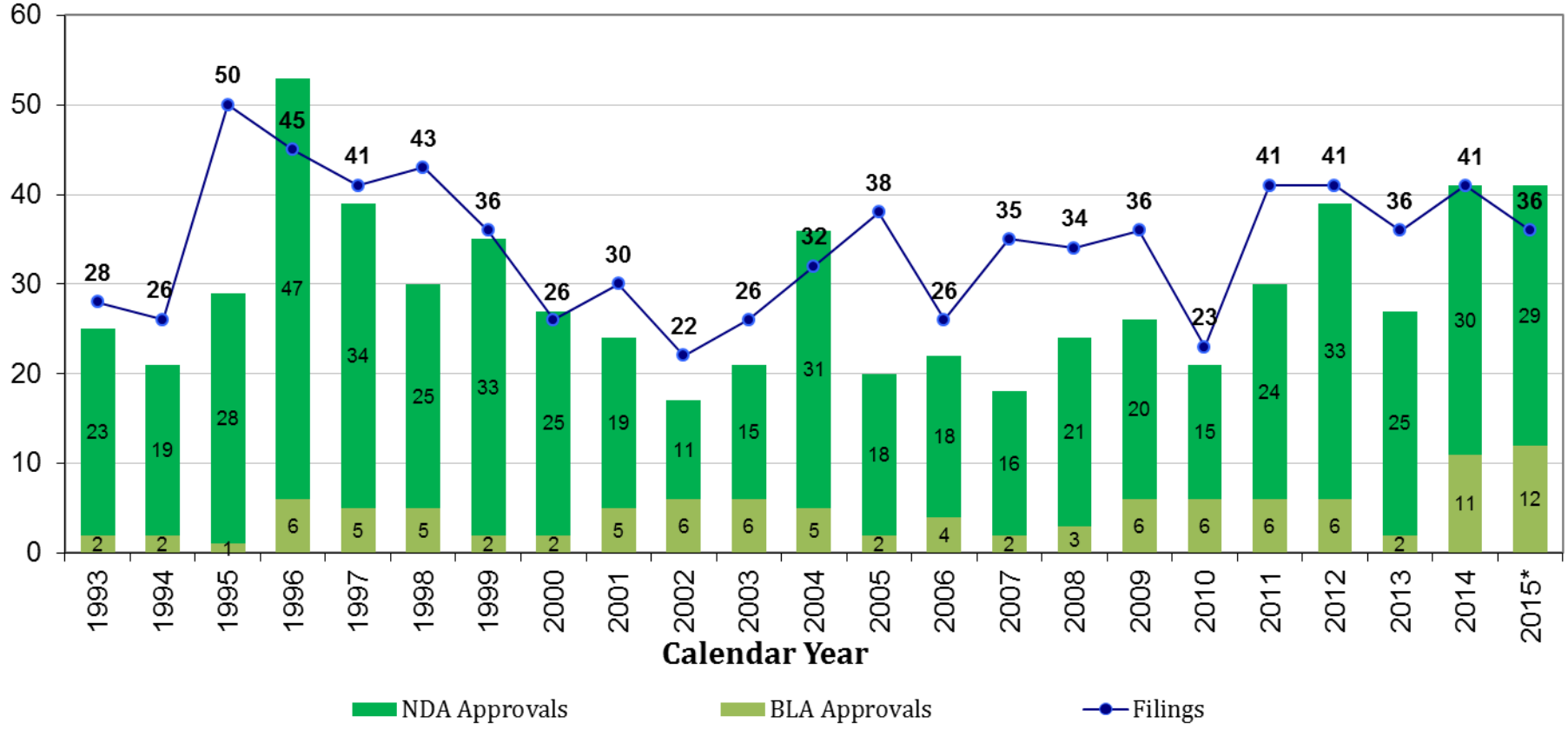
Data represent 12 month period of July 1st - June 30th

CDER PDUFA
Formal Meeting Requests



Data as of 9/30/2015

CDER NME NDAs/BLAs† Filings and Approvals as of 12/9/15

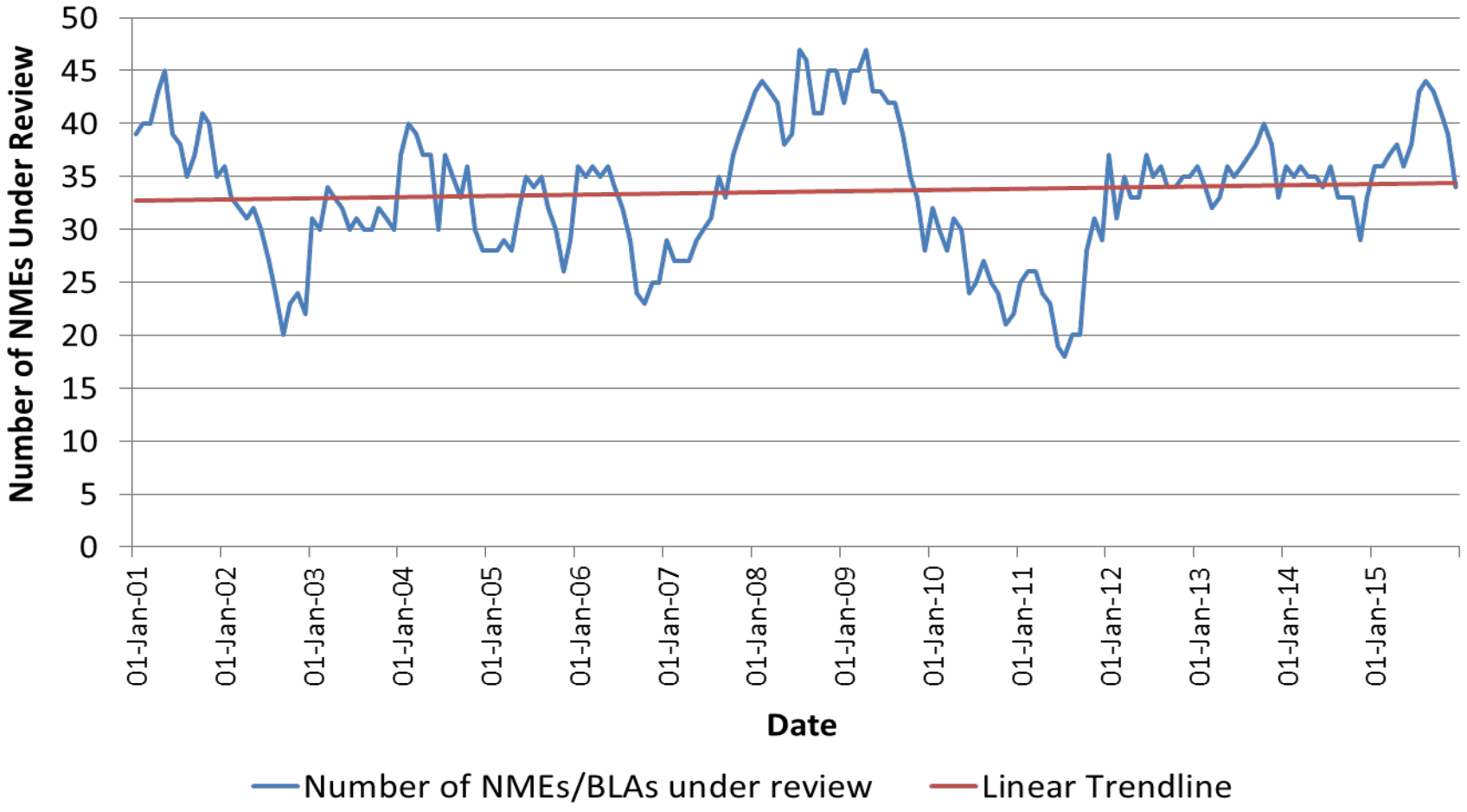


† Multiple applications pertaining to a single new molecular/biologic entity are only counted once. Original BLAs that do not contain a new active ingredient are excluded.

This information is accurate as of December 9, 2015. In rare instances, it may be necessary for FDA to change a drug's new molecular entity (NME) designation or the status of its application as a novel new biologics license application (BLA). For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug's designation or the status of an application as a novel BLA, the Agency intends to communicate the nature of, and the reason for, any revisions as appropriate. This note applies to all references to NME/Original BLAs in this presentation.

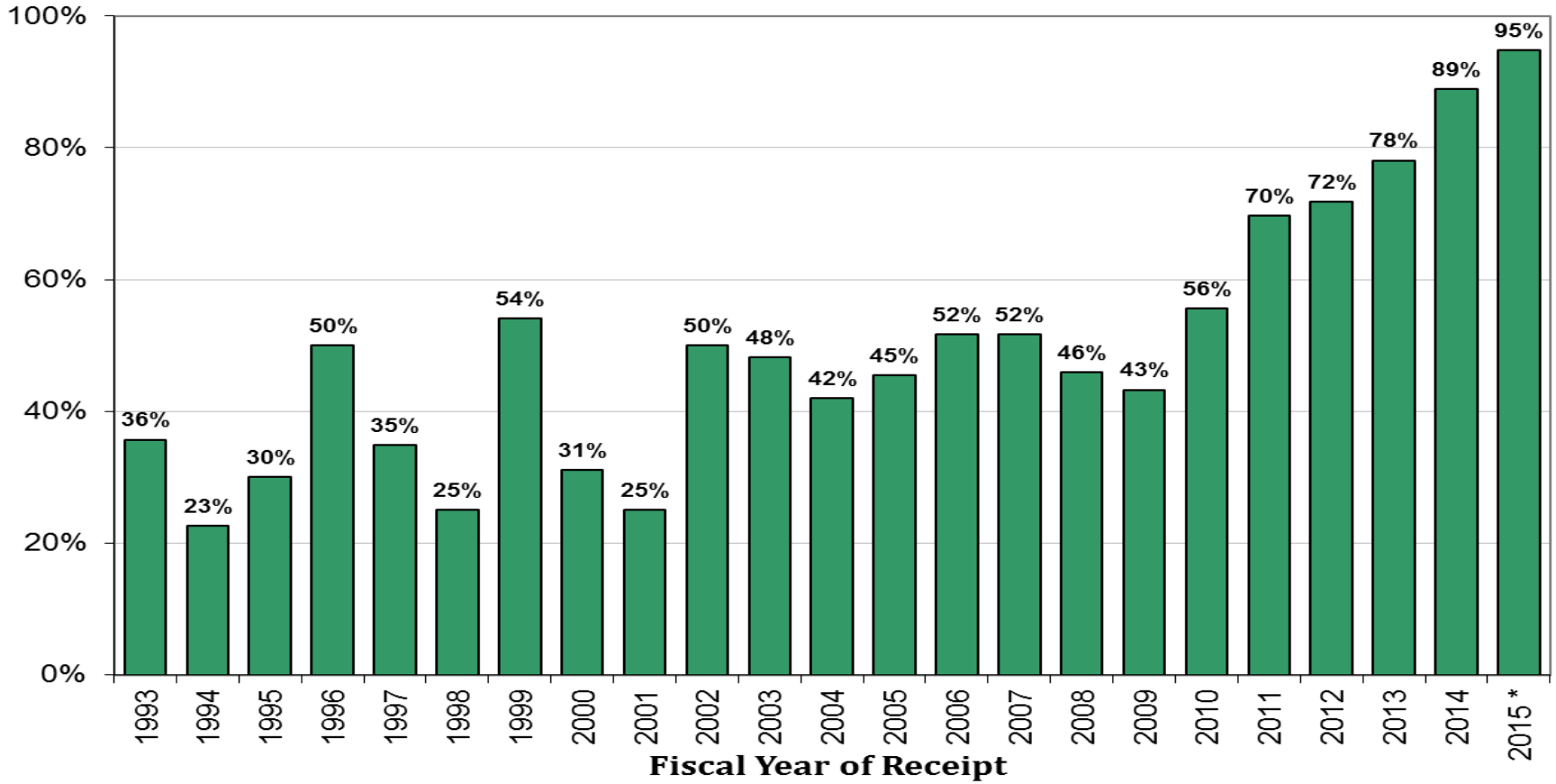
*Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.

Number of NMEs Concurrently Under Review



* Data as of 11/30/2015

CDER NME NDAs/BLAs† First Action Approval Rate



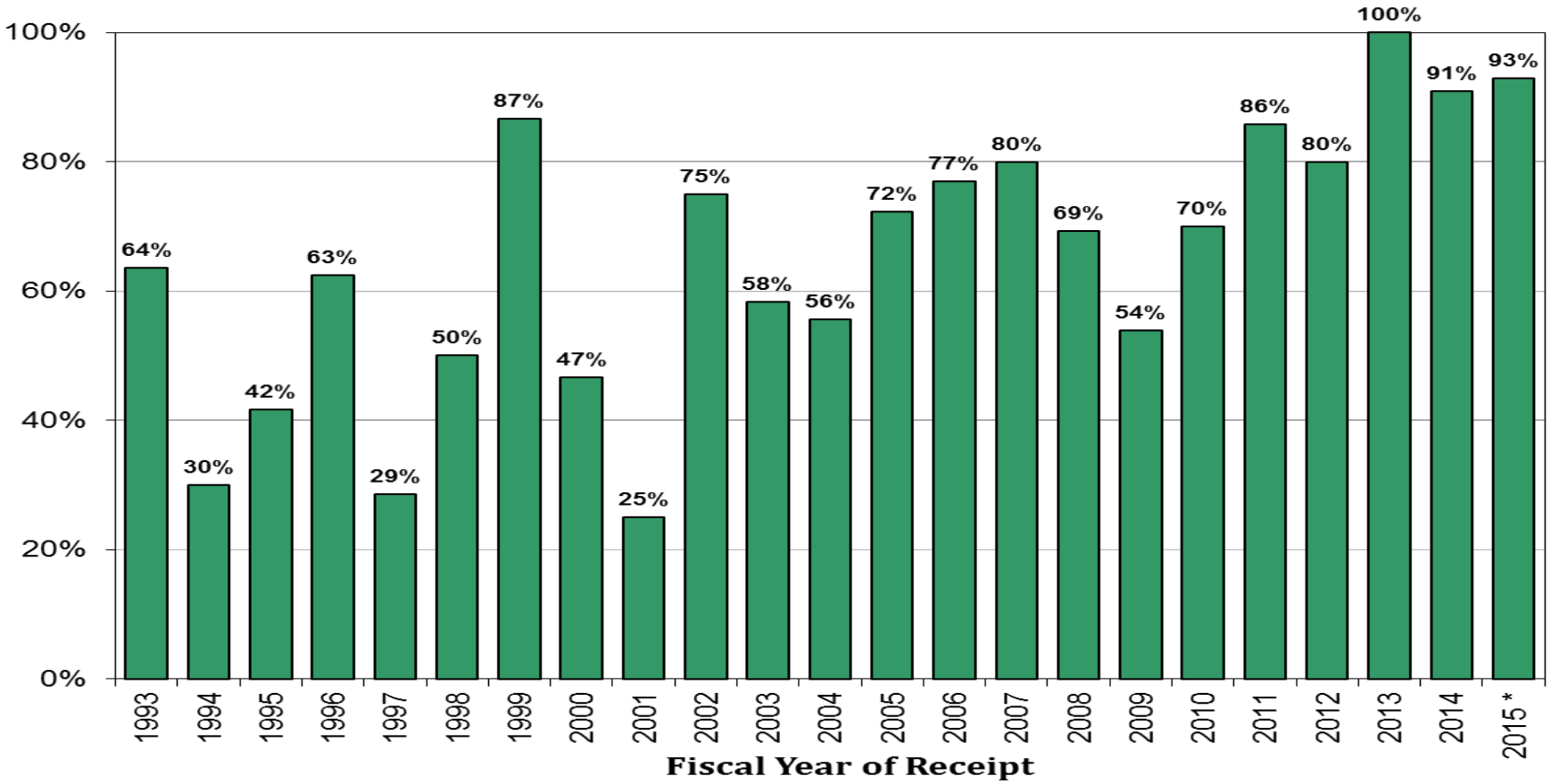
Data as of 12/9/2015

† Multiple applications pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.
Percentages exclude pending applications from the denominator.

* FY 15 Cohort has 25 pending applications.

CDER First Action Approval Rates For Priority NME NDAs/BLAs†



Data as of 12/9/2015

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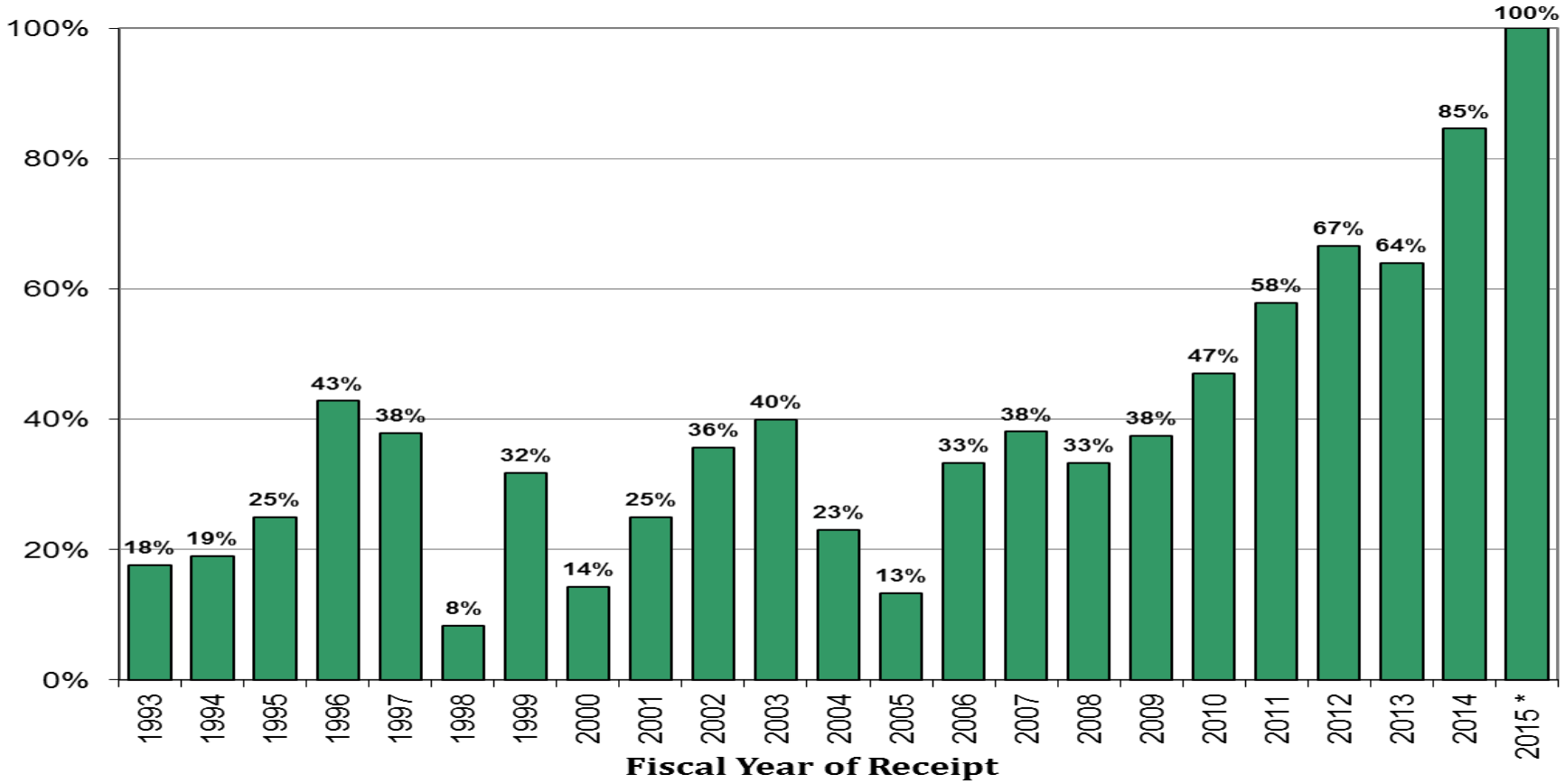
† Original BLAs that do not contain a new active ingredient are excluded.

Percentages exclude pending applications from the denominator .

* FY 15 Cohort has 11 pending priority applications.

CDER First Action Approval Rates For Standard NME NDAs/BLAs†



Data as of 12/9/2015

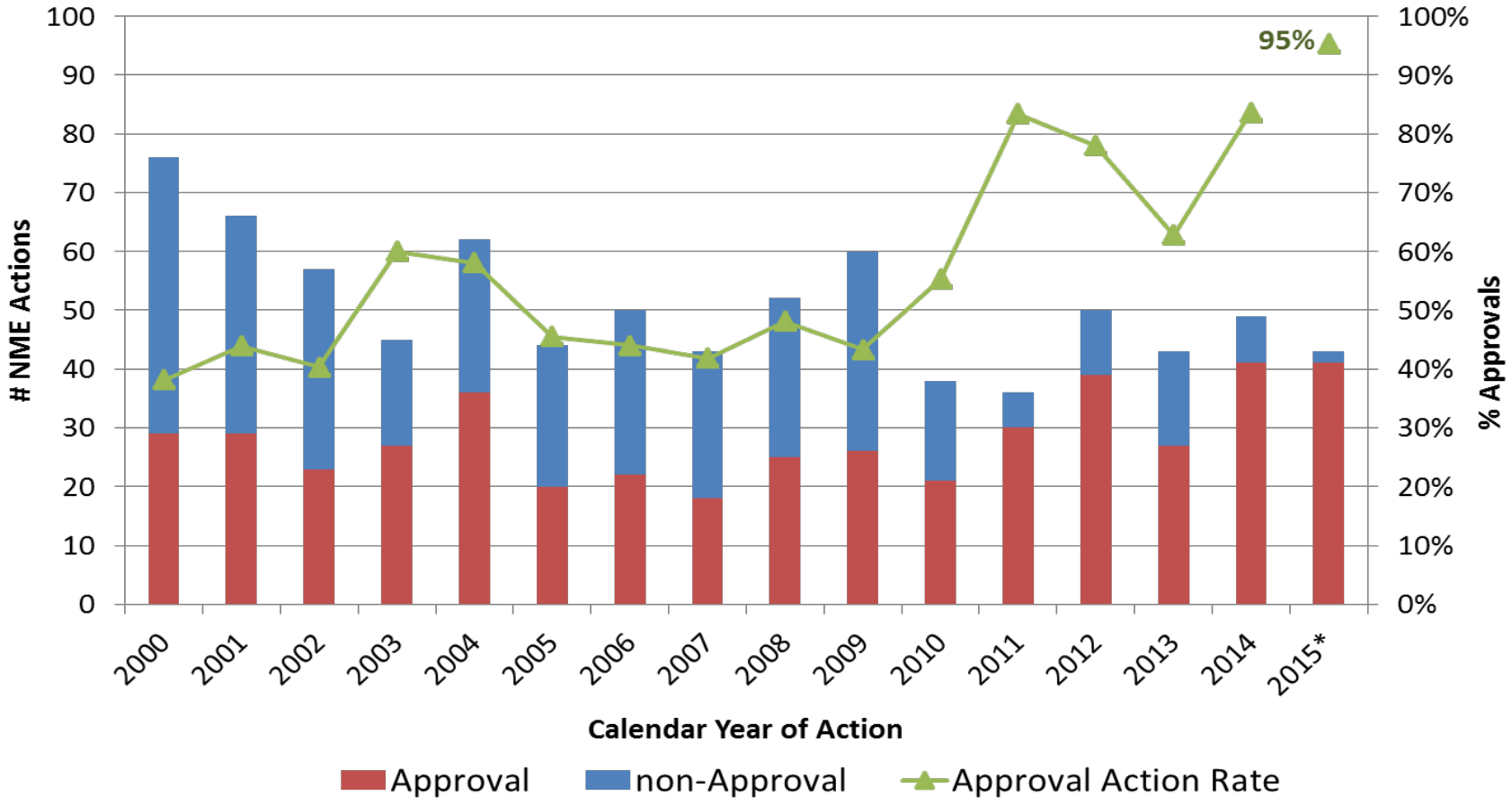
† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

Percentages exclude pending applications from the denominator.

* FY 15 Cohort has 14 pending standard applications.

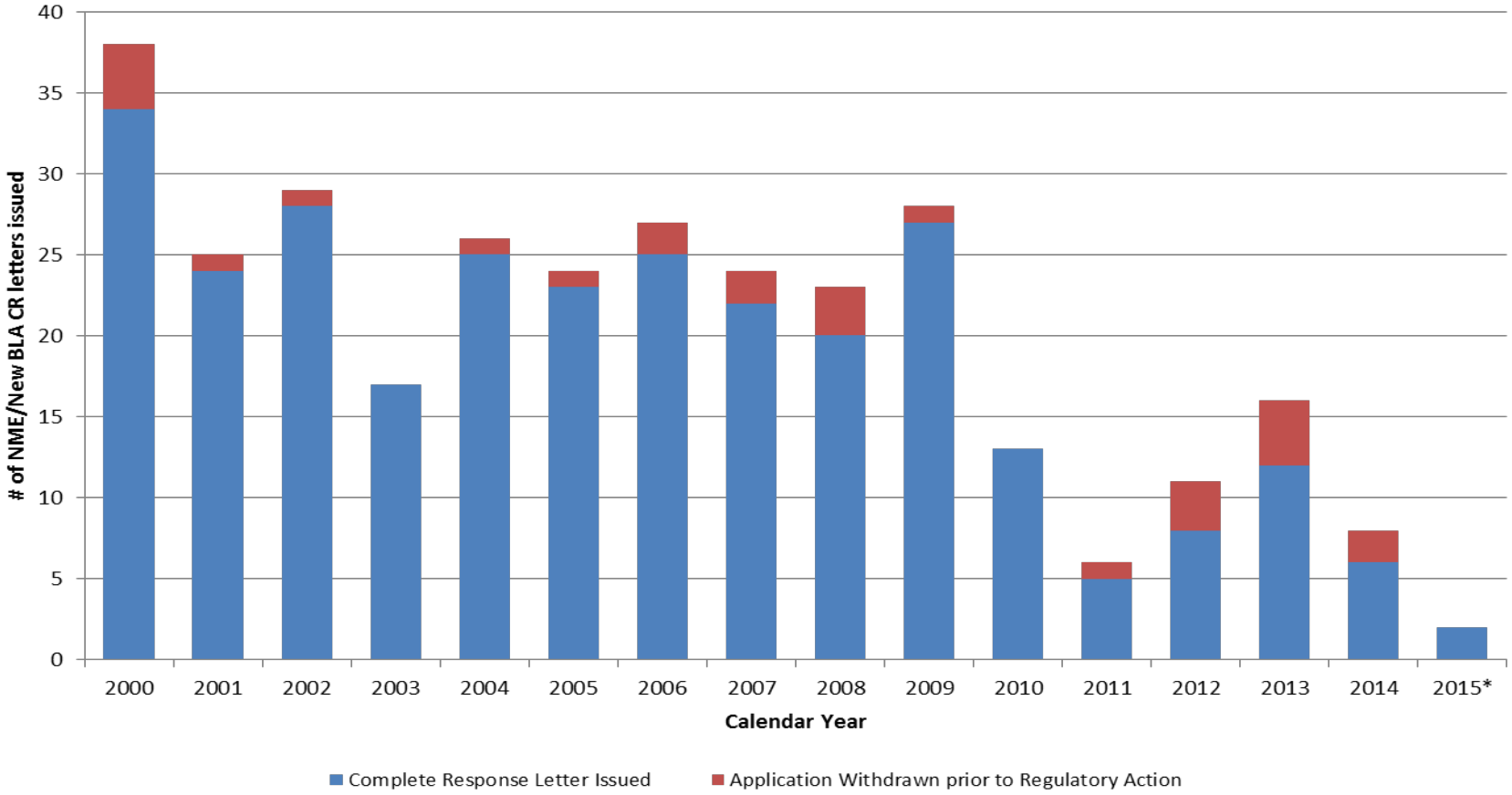
NME Actions and Approvals



*Data as of 12/09/2015

Includes discrete actions on a given date for an active ingredient which, if approved, would constitute a new molecular entity. Actions for original submissions and resubmissions as well as actions for new BLAs are included. Multiple actions which occur on the same date for multiple dosage forms or indications are counted as a single regulatory action.

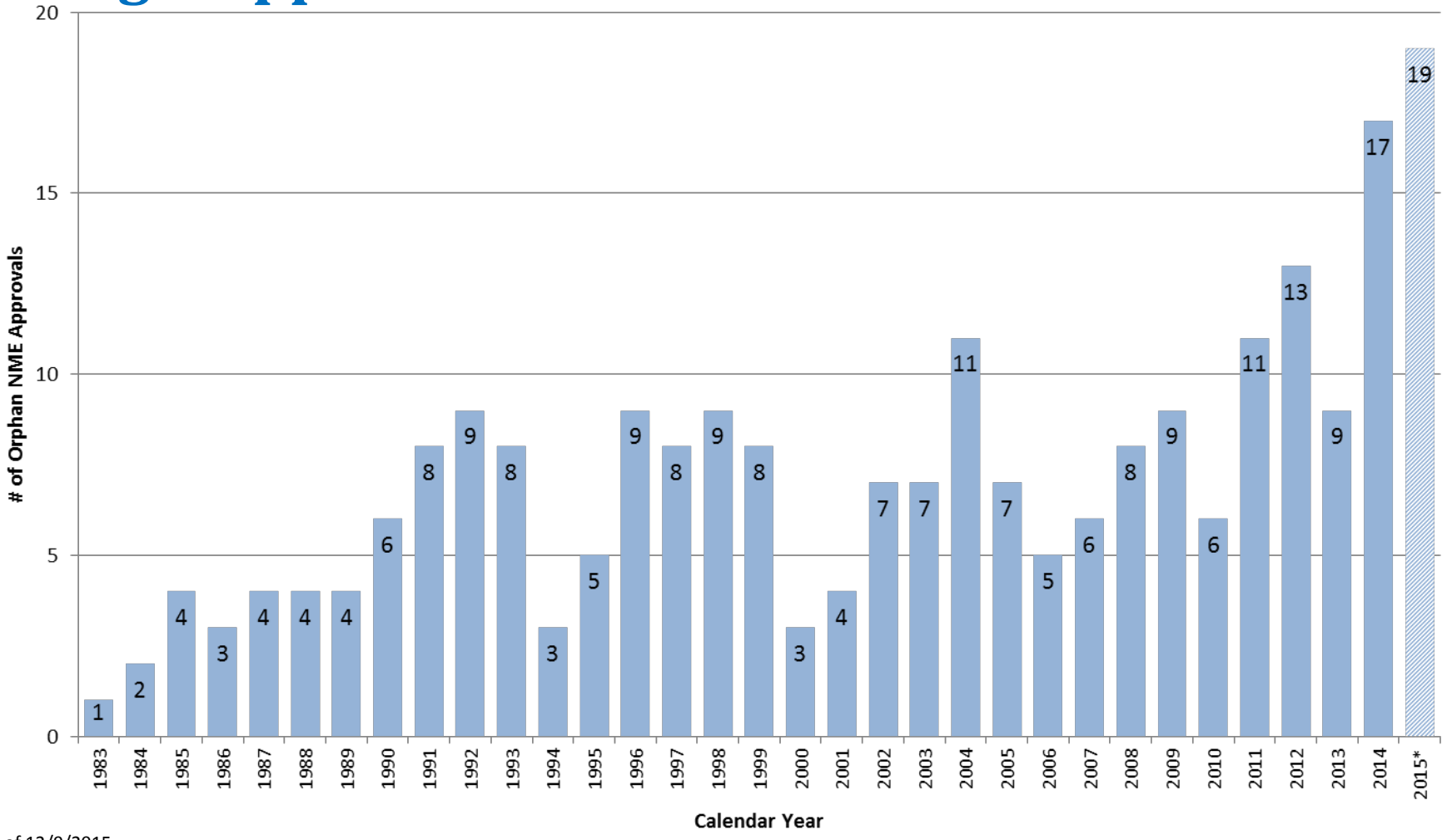
CDER NME/New BLA Complete Response* Letters Issued



Data as of 11/30/2015

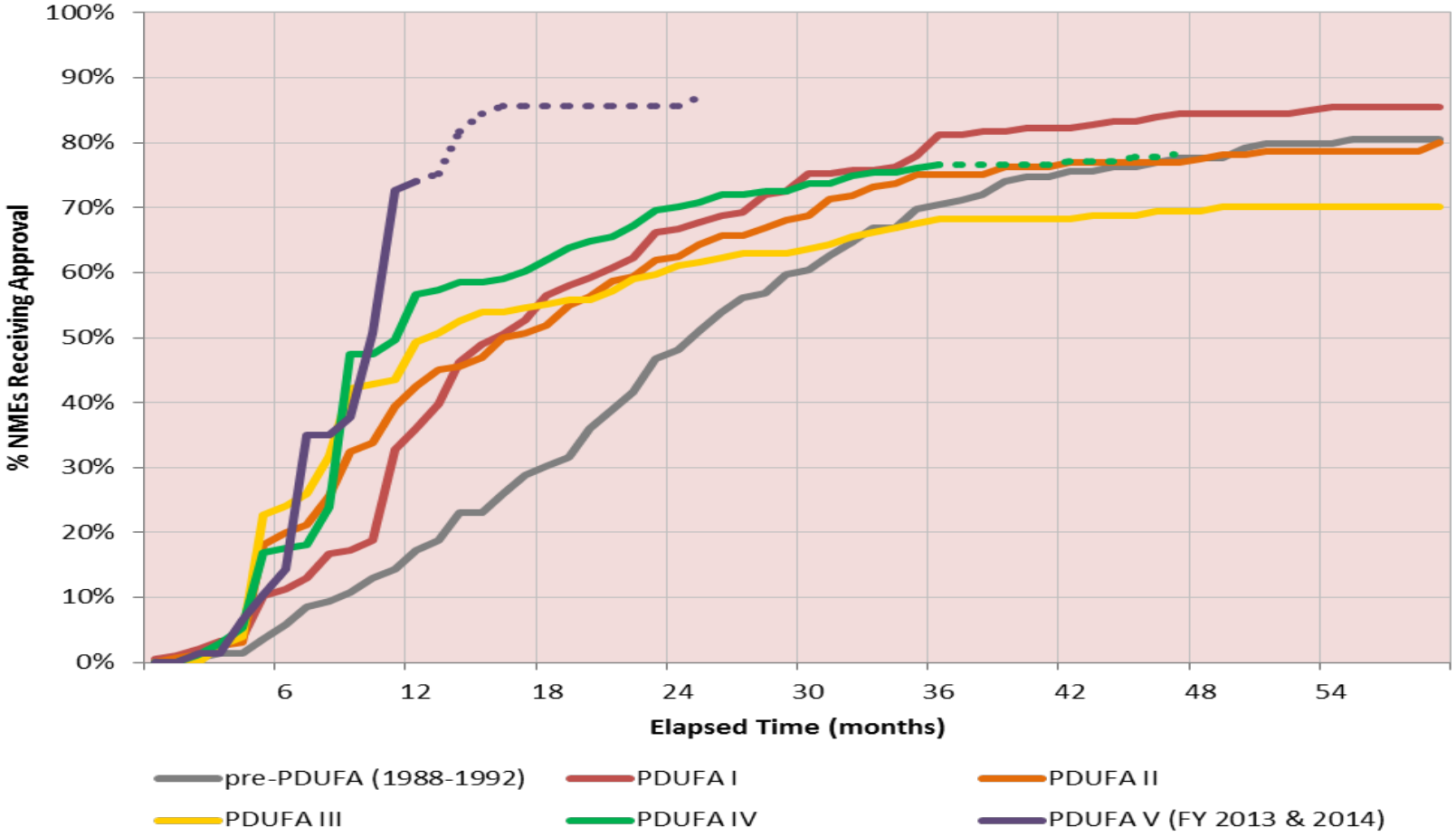
* Complete Response letter figures include “approvable” and “not approvable” letters issued for NDA actions prior to August 11, 2008, the date the Complete Response Letter rule was finalized.

CDER Orphan NME and New Biologic Approvals



Data as of 12/9/2015

CDER New Molecular Entity Approval Rates by PDUFA Cohort

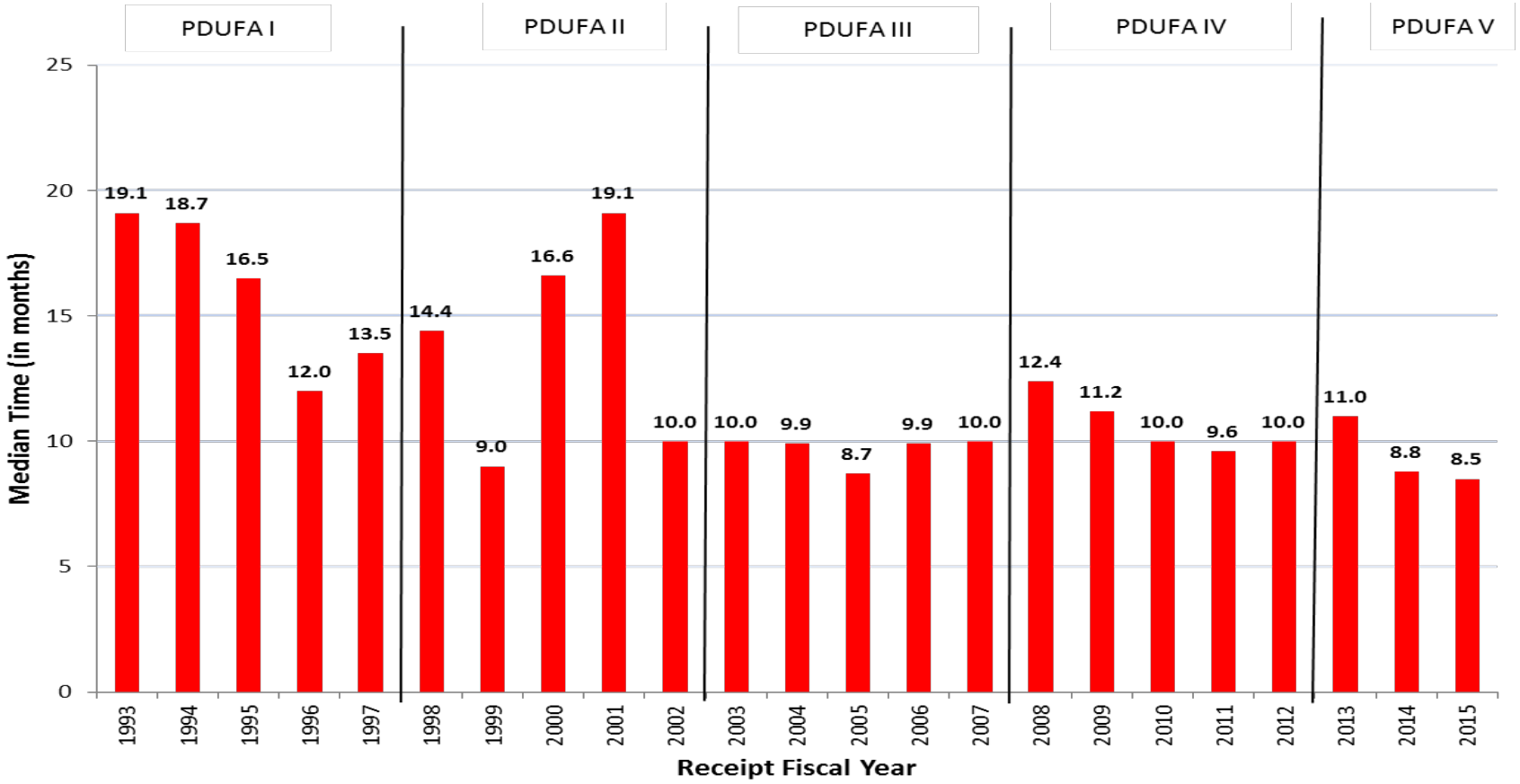


* Data as of 11/30/2015 PDUFA IV estimates based on 77 NMEs submitted in FY 2013 - 2014 (it is too early to estimate performance on FY 2015 submissions). Projection estimates account for actions to date and elapsed time to date for non-approvals and assume an additional 6 months of review time at a minimum for unapproved applications after resubmission. Currently no unapproved NMEs from the FY 2013 - 2014 submission cohort are pending review as of 11/30/2015

Why are first-cycle NME approval rates so high?

- CDER has not changed its interpretation of the statutory standard for approval – we are not a "rubber stamp"
- Factors that may be contributing
  - FDA guidance/meetings during IND to clarify expectations for development programs – improves quality of NDAs/BLAs
  - NME Program – complete applications at time of filing and more time for interactions with sponsor to address deficiencies
  - Targeted therapies – greater benefit/less risk in selected patients
  - More orphan drugs – alters benefit/risk balance
  - BT designation – "all-hands on deck" for sponsor and FDA
  - Focus of sponsors away from "me too" drugs and diseases with available treatment options with less favorable B/R balance
    - Not necessarily a good outcome from a public health perspective
  - Other factors?

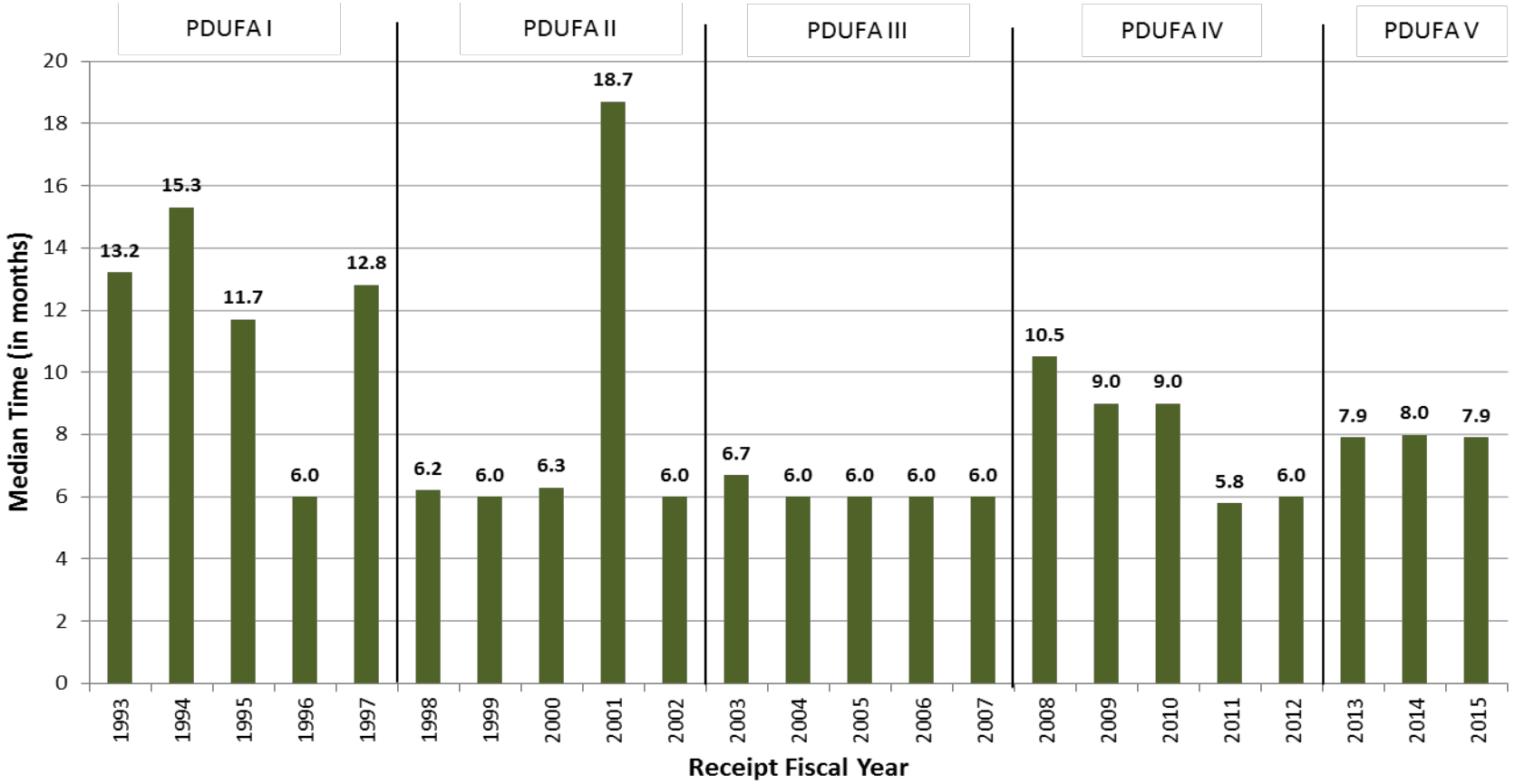
CDER Overall NME NDA/BLAs† Median Total Time to Approval



Data as of 12/9/2015

† Original BLAs that do not contain a new active ingredient are excluded.

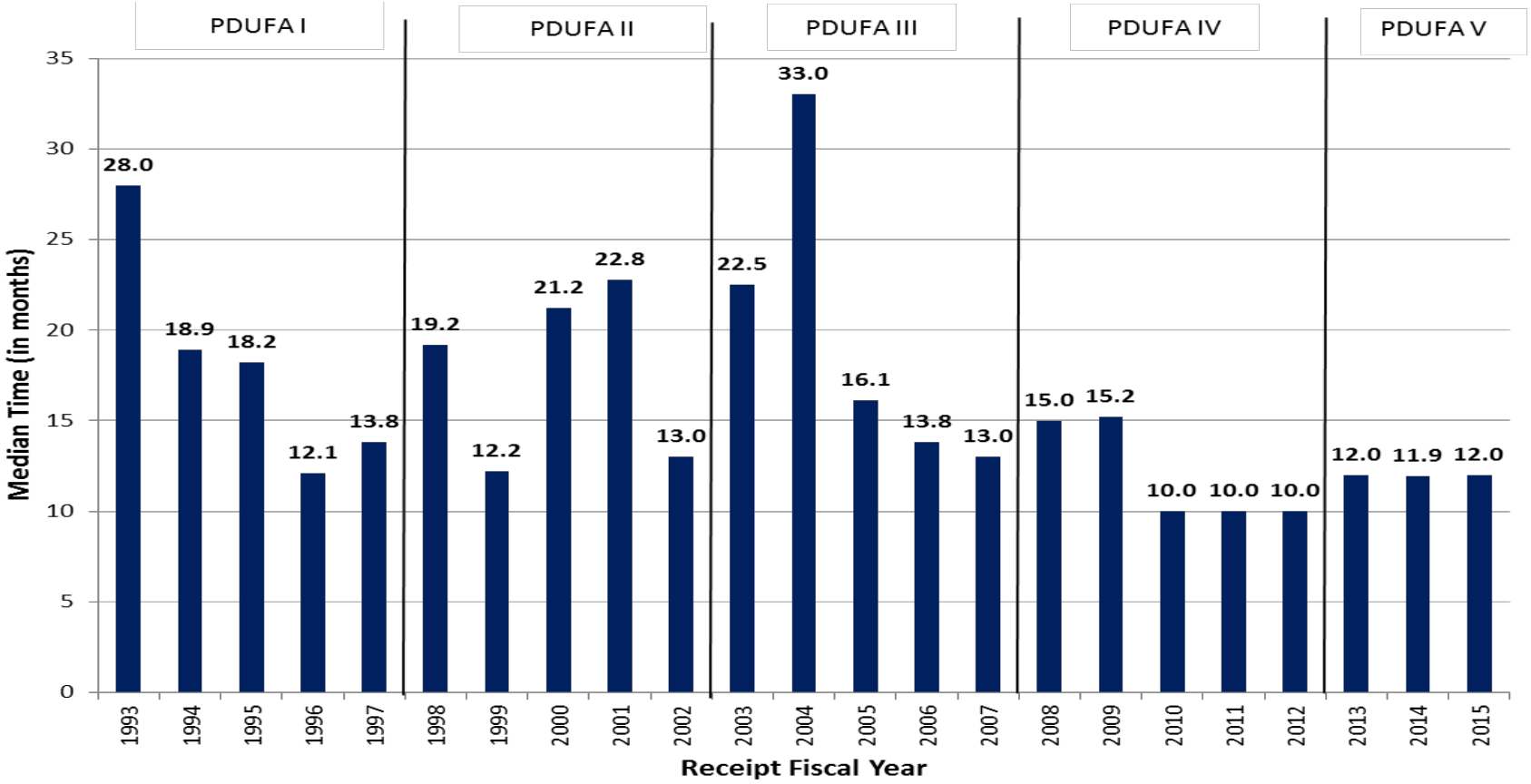
CDER Priority NME NDAs/BLAs† Median Total Time to Approval



Data as of 12/9/2015

† Original BLAs that do not contain a new active ingredient are excluded.

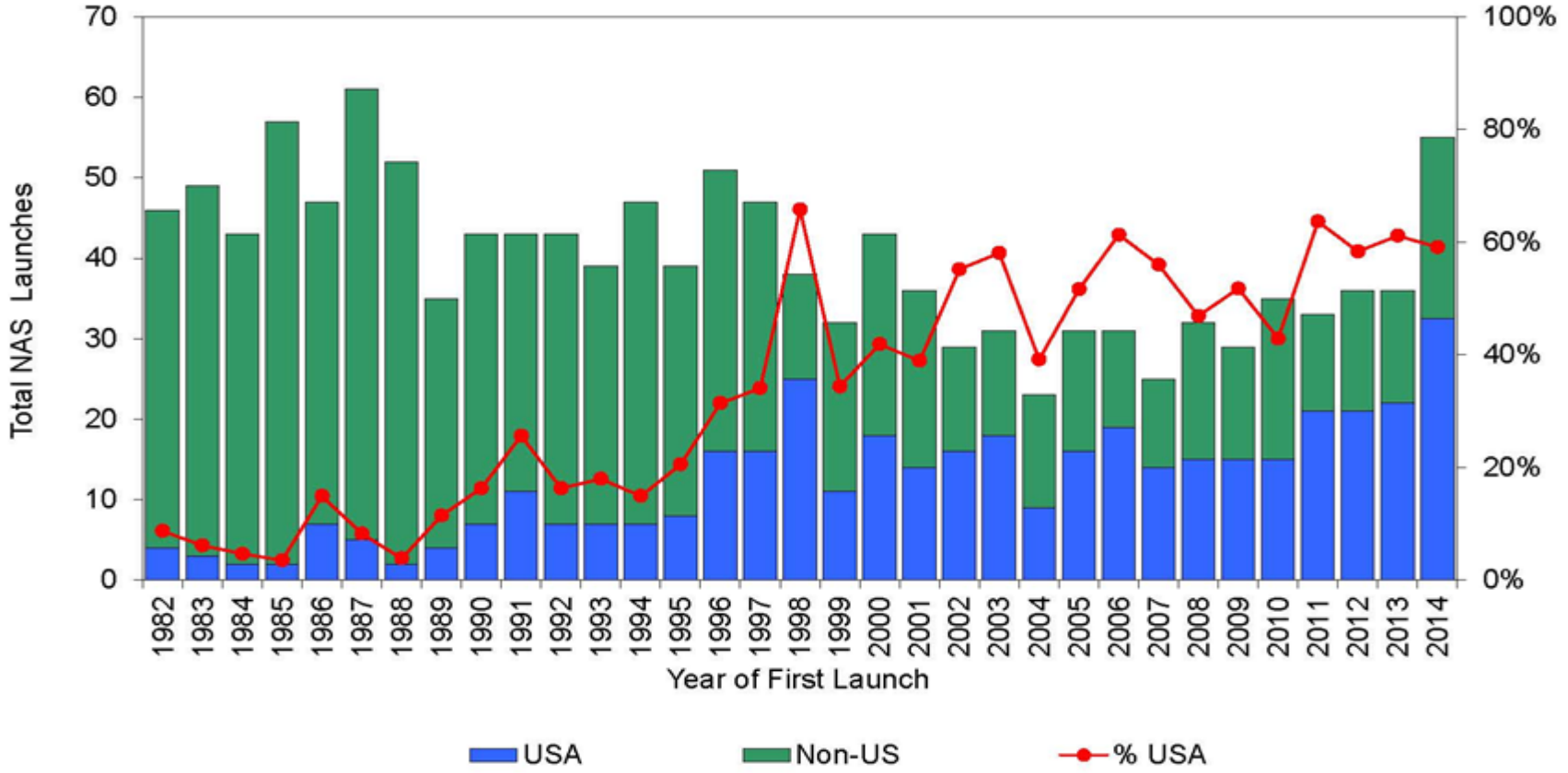
CDER Standard NME NDA/BLAs† Median Total Time to Approval



Data as of 12/9/2015

† Original BLAs that do not contain a new active ingredient are excluded.

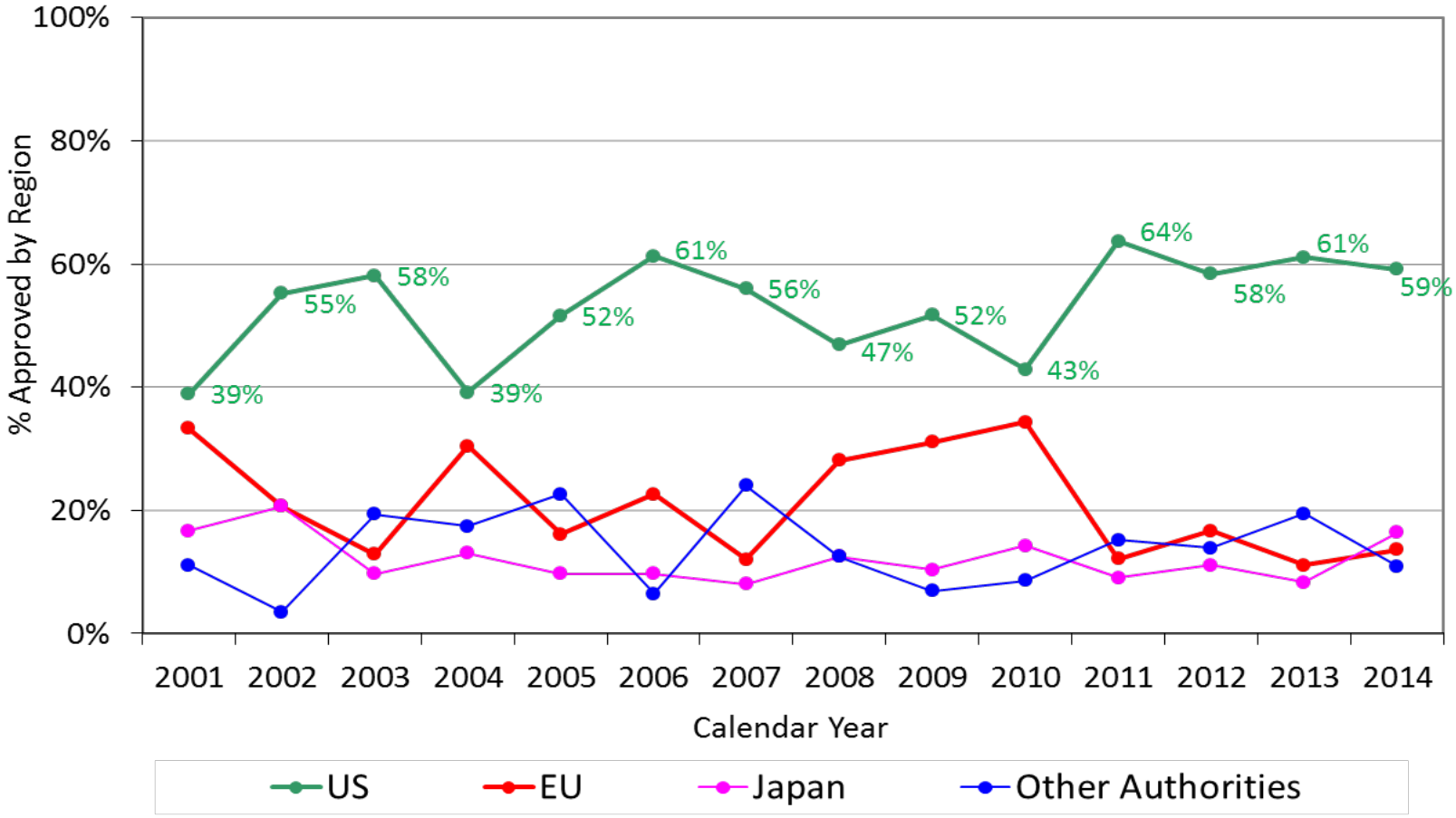
USA Share of New Active Substances Launched on World Market



Data as of 11/30/2015

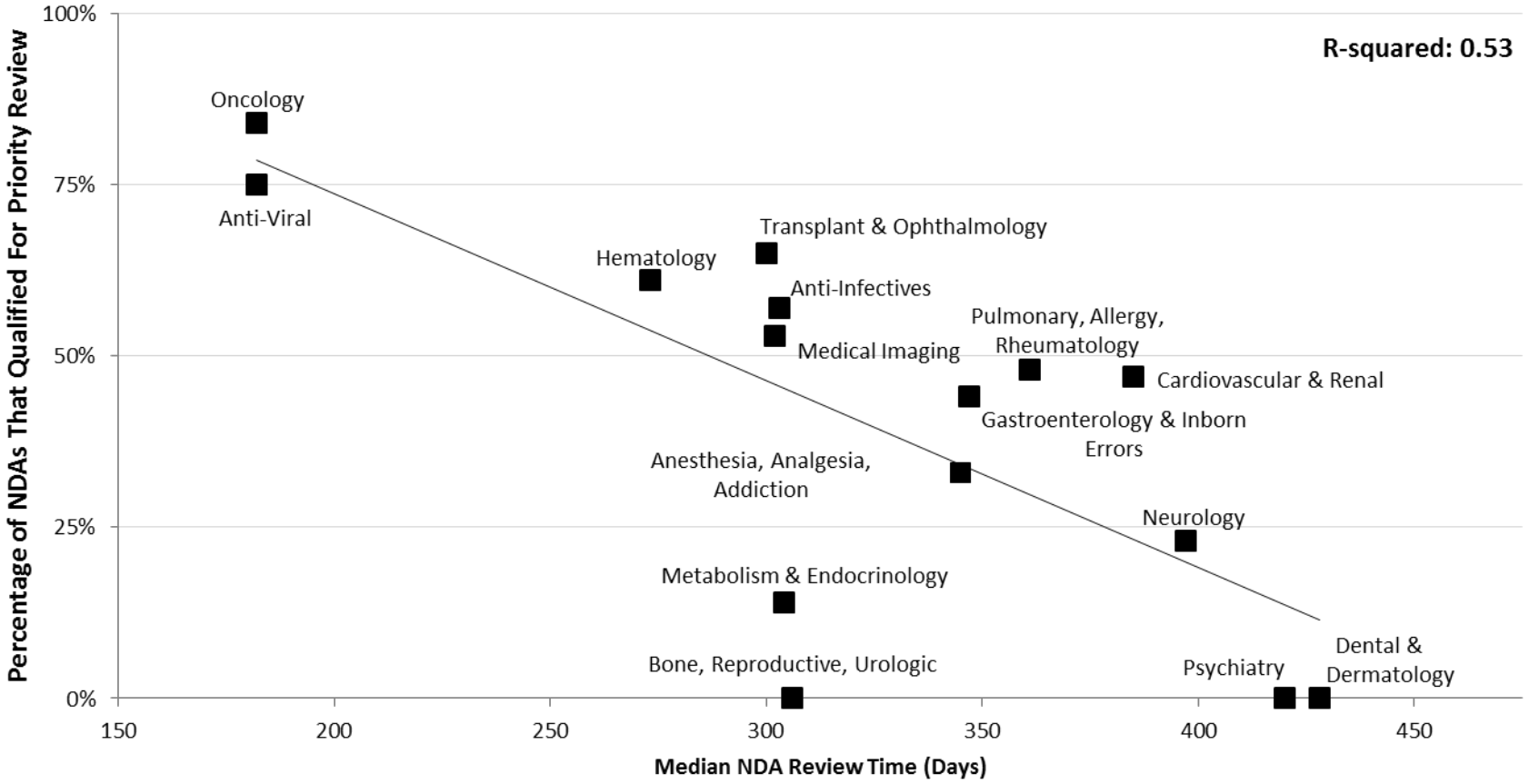
Source: *Scrip Magazine* (1982 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2014)

Global New Active Substances First Launches by Region 2001 – 2014



Source: *Scrip Magazine* (2001 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2014)

Median NDA Review Times AND Priority Reviews Received By Drug Review Division



Snapshot of CY 2015
NME NDAs/BLAs† Drug Approvals (1/3)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Accelerated Approval	Orphan Drug	Breakthrough Therapy	QIDP
SAVAYSA										
COSENTYX										
NATPARA										
IBRANCE										
LENVIMA										
FARYDAK										
AVYCAZ										
CRESEMBA										
UNITUXIN										
CHOLBAM*										
CORLANOR										
KYBELLA										
VIBERZI										
KENGREAL										

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

QIDP - Qualified Infectious Disease Product

* Cholbam- Currently listed as not first in class, but subject to change. The first in class status for cholic acid is still under consideration by the DASH LOE committee. Approved in 2014 in EU for SED but not PE

Snapshot of CY 2015
NME NDAs/BLAs† Drug Approvals (2/3)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Accelerated Approval	Orphan Drug	Breakthrough Therapy	QIDP
ORKAMBI										
ENTRESTO										
REXULTI										
PRALUENT										
ODOMZO										
DAKLINZA										
ADDYI										
REPATHA *										
VARUBI										
XURIDEN										
VRAYLAR										
LONSURF										
TRESIBA										

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

QIDP - Qualified Infectious Disease Product

*Repatha was submitted with two indications. One indication received Orphan designation while the other did not. Application received a priority review due to redemption of a PRV.

Snapshot of CY 2015
NME NDAs/BLAs† Drug Approvals (3/3)

Trade Name	Met PDUFA Goal Date*	Approved on First Cycle	Priority Approval	Fast Track	First in Class	Approved First in the U.S.	Accelerated Approval	Orphan Drug	Breakthrough Therapy	QIDP
ARISTADA										
PRAXBIND										
VELTASSA										
YONDELIS										
STRENSIQ										
NUCALA										
GENVOYA										
COTELLIC										
TAGRISSO										
DARZALEX										
NINLARO										
PORTRAZZA										
EMPLICITI										
KANUMA										

Data as of 12/9/2015

† Multiple submissions pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded.

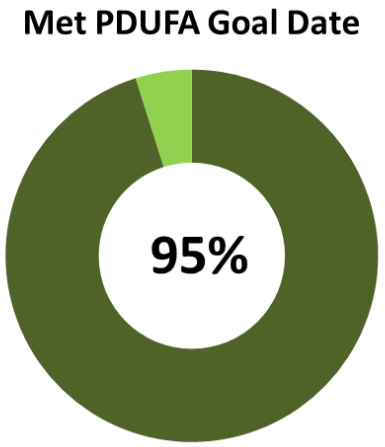
* A PDUFA Goal Date is marked as met if the NME is acted upon within its approval cycle due date.

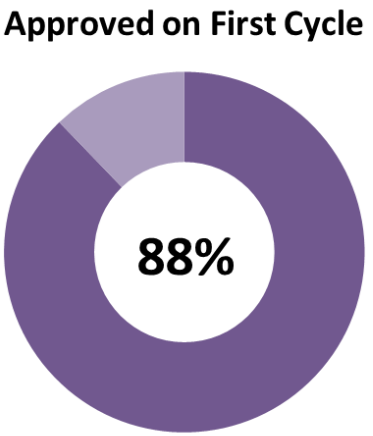
QIDP - Qualified Infectious Disease Product

In CY 2015, CDER Continued To Ensure The Efficiency Of First Cycle Review

- All but two (95%) of the novel drugs approved to date in CY15 met their PDUFA goal dates for the approval review cycle

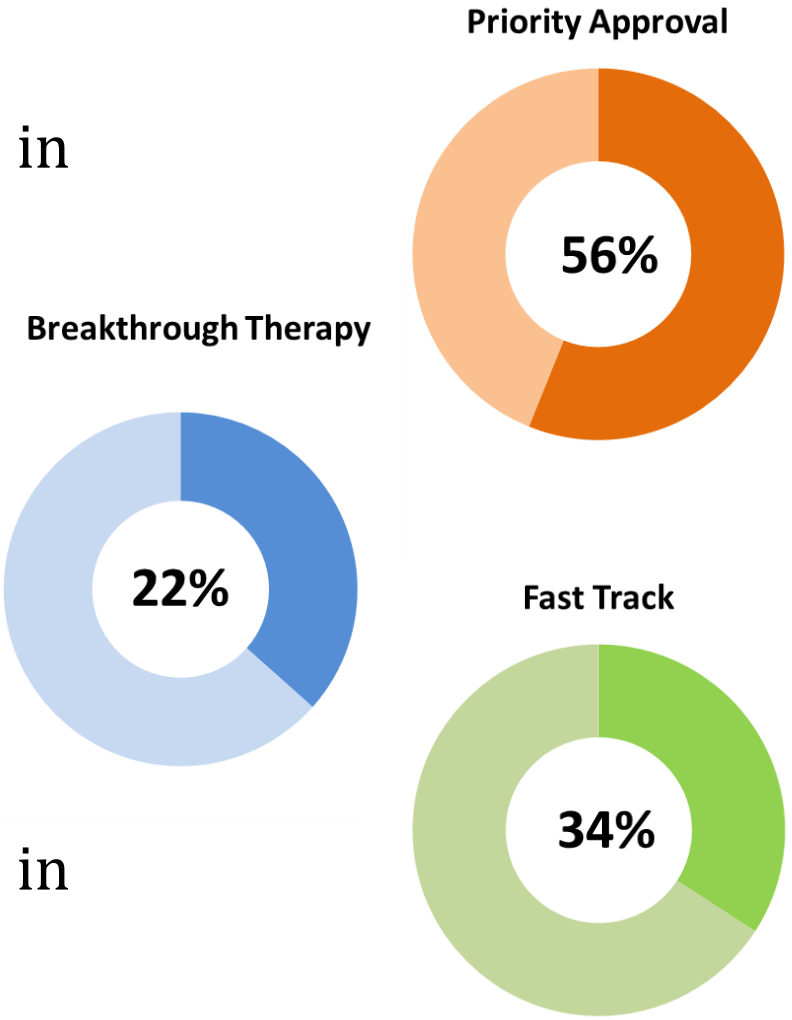
- Almost nine out of ten of the novel drugs (88%) approved to date in CY15, were approved in the first review cycle





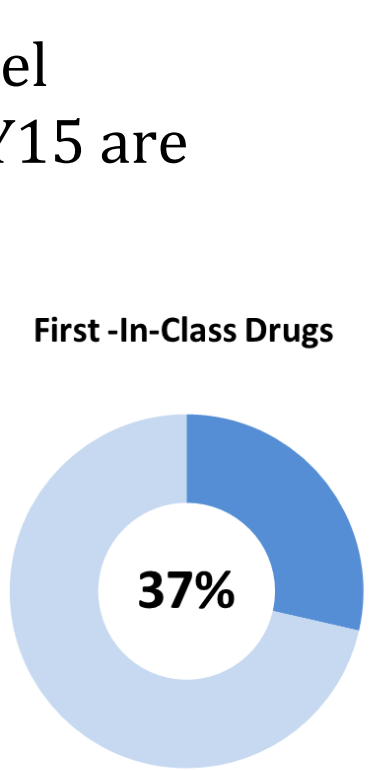
CDER Ensures That Novel Drugs Receive Expedited Review

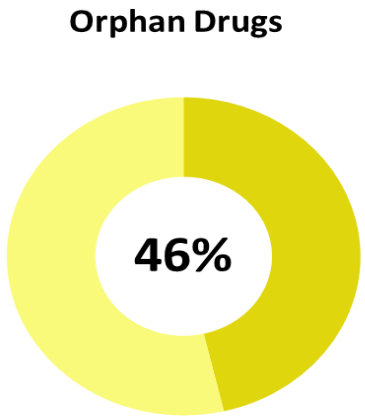
- More than half (56%) of the novel drugs approved to date in CY15were approved under Priority Review
- Almost one – quarter (22% of the novel drugs approve to date in CY15 received Breakthrough Therapy designation
- About a third (34%) of the novel drugs approved to date in CY15 received Fast Track designation

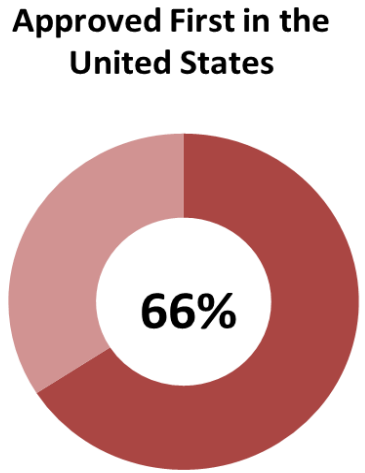


2015 Continues A Strong Track Record For Drug Innovation

- Nearly half (46%) of the novel drugs approved to date in CY15 are for rare diseases
- Over one-third (37%) of the novel drugs approved to date in CY15 are the first in their class
- Two-thirds (66%) of the novel drugs approved to date in CY15 were first approved in the U.S.







Selected PDUFA V/FDASIA Programs That Impact Drug Development and Review

Review Program for NME NDAs and Original BLAs

Goal

- "Improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics." (PDUFA V Goals Letter)

Concept

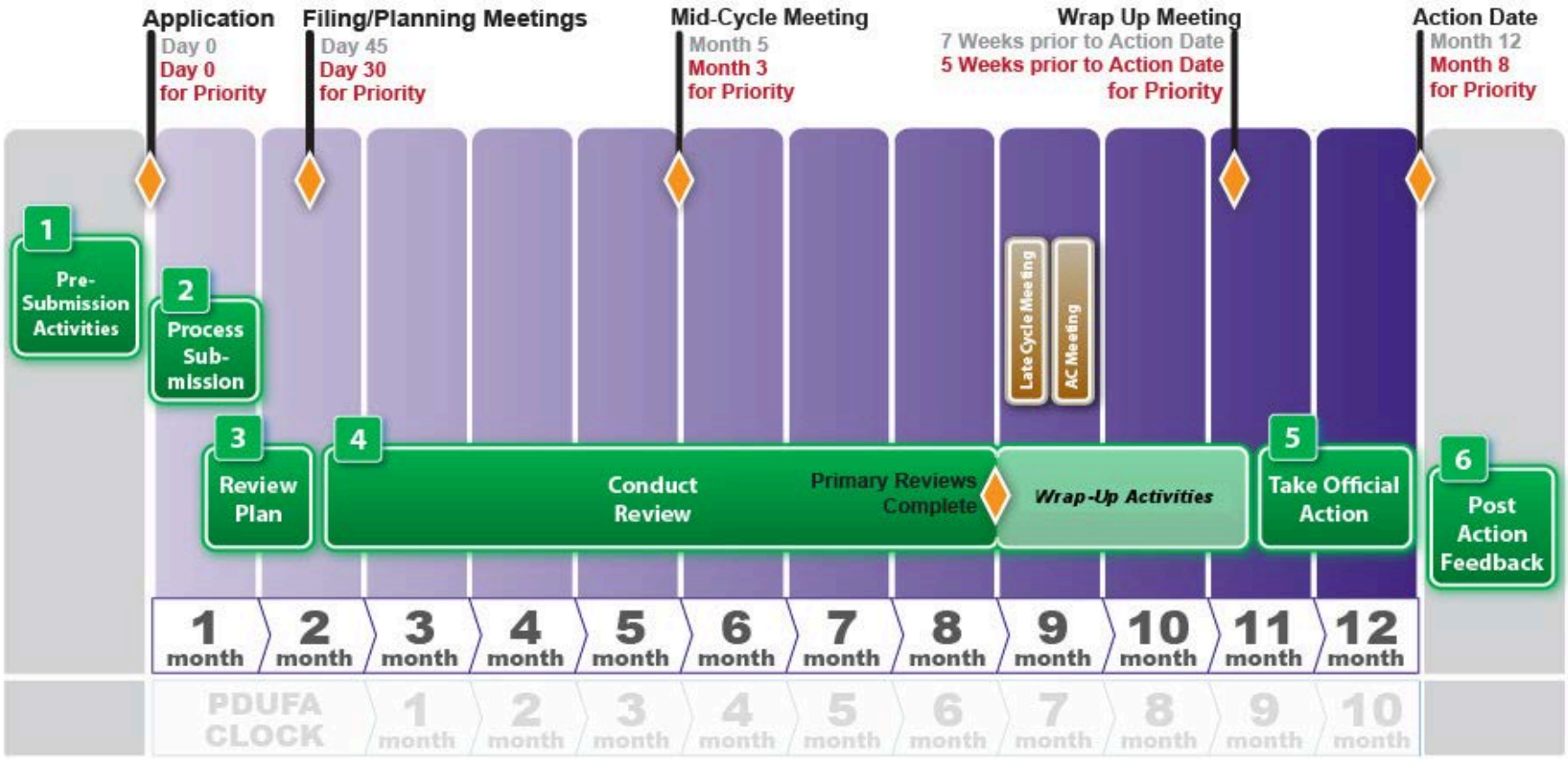
- Better planning before application submission, submission of complete applications, improved communication and transparency between applicant and review team during review, and additional review time will improve the efficiency of the first review cycle, which may decrease the number of additional review cycles prior to approval.

Review Program for NME NDAs and Original BLAs

Components

- Pre-submission meeting strongly encouraged
- Complete application at time of submission; incomplete subject to RTF
- 60-day filing review period "off the clock"
- 74-Day Letter
  - Planned review timeline, planned date of internal mid-cycle meeting, preliminary plans on need for AC meeting, early communication of deficiencies/information requests
- Mid-Cycle Communication
  - Within 2 weeks of internal mid-cycle meeting
  - Communication of significant issues identified to date/information requests, preliminary thinking on risk management/REMS, proposed dates for late-cycle meeting, updates on AC plans
- Discipline review letters
  - Summarize preliminary findings/deficiencies by discipline
- Late-cycle meeting (LCM)
  - Focus on information sharing, planning for AC, and planning for the remainder of review

Sample Program Review Timeline – Standard Application



Cumulative Activity in the Program

	FY2013 (9/30/13)	FY2014 (9/30/14)	FY2015 (9/30/15)	Through 11/30/15
PSMs	42	96	137	**141**
Receipts	53 33 NDAs 20 BLAs	106 68 NDAs 38 BLAs	166 106 NDAs 60 BLAs	**174** **110 NDAs** **64 BLAs**
RTFs	2	3	4	**4**
Day 74	44	98	157	**163**
MCCs	33	80	135	**150**
DR letters	5	8	10	**10**
LCMs	17	64	111	**121**
FCAs	6 4 APs 0 CRs 2 WDs	64 46 APs 14 CRs 4 WDs	115 92 APs 18 CRs 5 WDs	**133** **108 APs** **20 CRs** **5 WDs**
PAIs	6 3 FDA 3 applicant	106 56 FDA 50 applicant	196 103 FDA 93 applicant	**211** **108 FDA** **103 applicant**
Major Amendments received	3 3 APs	18 17 APs 1 CR	35 26 APs 2 CRs 7 Pending	**37** **26 APs** **2 CRs** **9 Pending**
Amendments	166	2684	4740	**5263**

1. Major Amendments are categorized by the quarter in which they were received. The status (AP, CR, Pending) reflects the status of each application as of close of FY2014

AP = Approval
CR = Complete Response
WD = Withdrawal After Filing

PSM = Pre-Submission Meeting
RTF = Refuse to File
MCC = Mid-Cycle Communication
LCM = Late-Cycle Meeting

FCA = First Cycle Action
PAI = Post Action Interview
Note: Because 3 applications were split at action, 48 applications generated 51 actions. Includes CDER as well as CBER data

Program Modifications to Address Learnings

- Mid-cycle communication
  - Intended to be an informal communication between FDA project manager/CDTL and sponsor
  - Meeting has taken on greater importance than anticipated
  - Often involves more attendees from sponsor and FDA
  - Internal FDA guidance modified to encourage providing sponsor with meeting agenda in advance to facilitate improved communication/discussion of preliminary review issues
- Program negotiation in PDUFA V pre-dated Breakthrough
  - Program "timeline" based on full 8 or 12-month review cycle
  - Original construct not well aligned with expedited reviews
  - Modifications of FDA desk reference guide posted on 10/20/14 to accommodate expedited reviews while still honoring Program commitments

Breakthrough Therapies

- FDASIA program to expedite development and approval of new drugs intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
- FDASIA endorsed and extended FDA's long-standing policy of expediting promising new drugs for serious and life-threatening conditions
- Final guidance "Expedited Programs for Serious Conditions––Drugs and Biologics" issued May 2014

Breakthrough Approvals to Date* (1)

- 2013
  - Gazyva: CLL
  - Imbruvica: Mantle Cell Lymphoma
  - Solvaldi: Chronic Hepatitis C
- 2014
  - Kalydeco, supplement: CF
  - Arzerra, supplement: CLL
  - Zykadia: NSCLC, alk+
  - Zydelig: CLL
  - Inbruvica, supplement: CLL
  - Promacta, supplement: Aplastic Anemia
  - Keytruda: Metastatic Melanoma
  - Ofev: Idiopathic Pulmonary Fibrosis
  - Esbriet: Idiopathic Pulmonary Fibrosis
  - Blincyto: ALL

* Data as of 12/9/2015

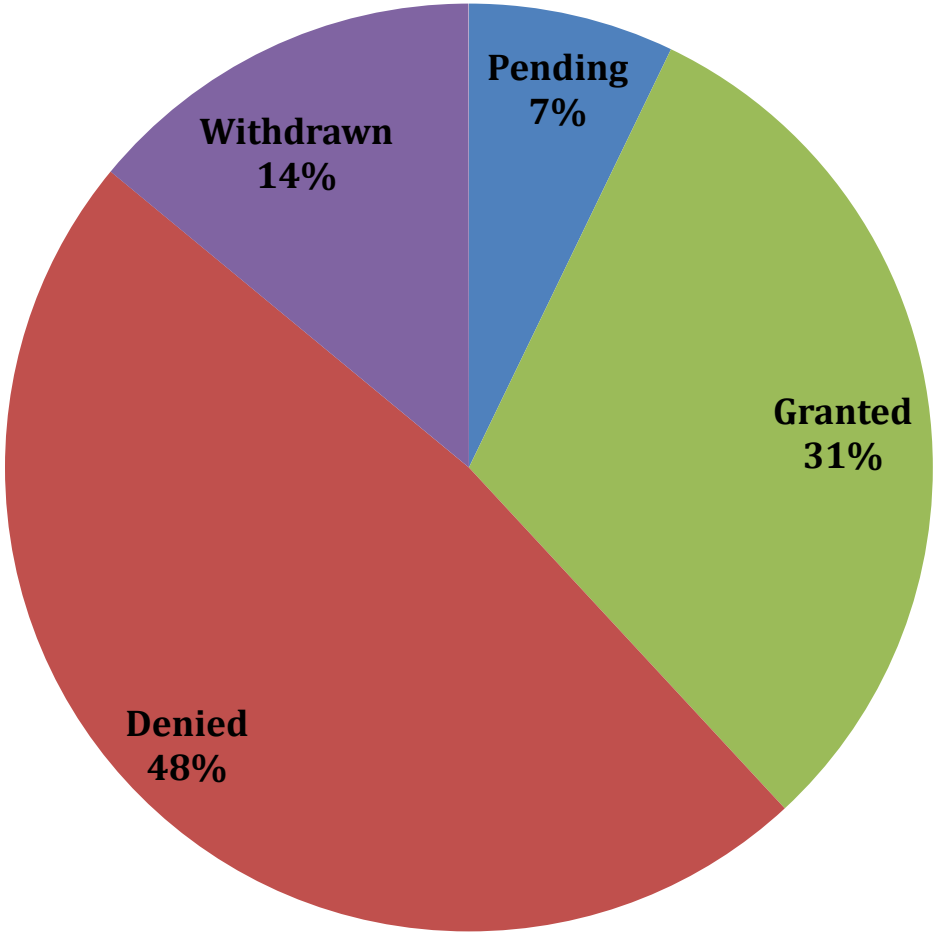
Breakthrough Approvals to Date* (2)

- 2015

-Ibrance: Metastatic Breast Cancer
-Orkambi: Cystic Fibrosis
-Xuriden: Hereditary Orotica Aciduria
-Imbruvica , supplement : CLL
-Lucentis , supplement : Diabetic Retinapathy
-Kalydeco :Cystic Fibrosis
-Eleya , supplement: Diabetic Retinopathy
-Rapamune, supplement: Lymphangioleiomyomatosis
-Technivie: HCV
-Keytruda, supplement: NSCLC
-Opdivo, supplement: NSCLC, Renal Cell Carcinoma
-Praxbind: Reversal of anticoagulant effects of dabigitran
-Strensiq: Hypophosphatasia
-Tagrisso: NSCLC
-Darzalex: Multiple Myeloma
-Empliciti: Multiple Myeloma
-Kanuma: Lysosomal Acid Lipase Deficiency

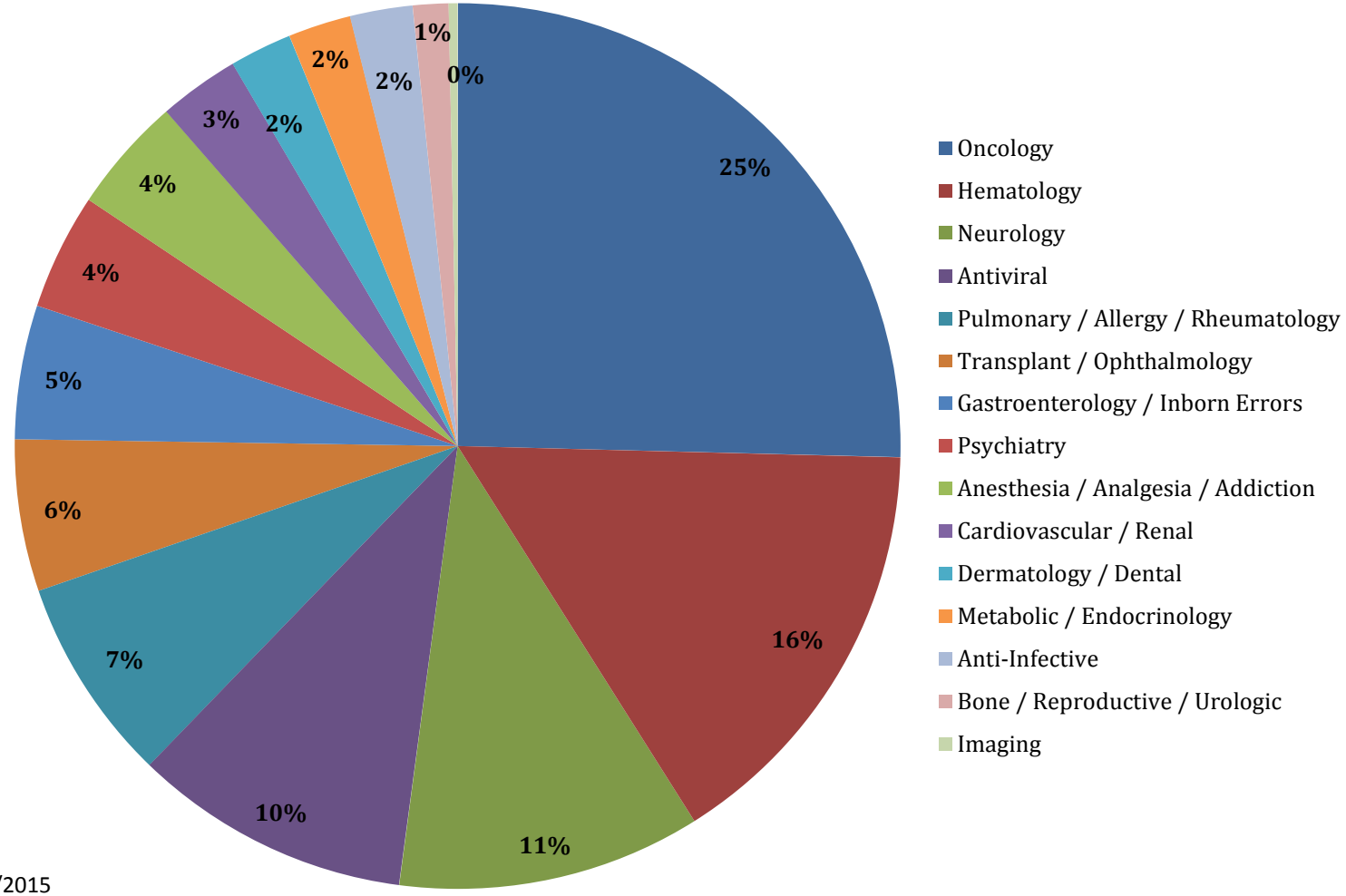
*Data as of 12/9/2015

Current Status of 307 CDER Breakthrough Therapy Requests



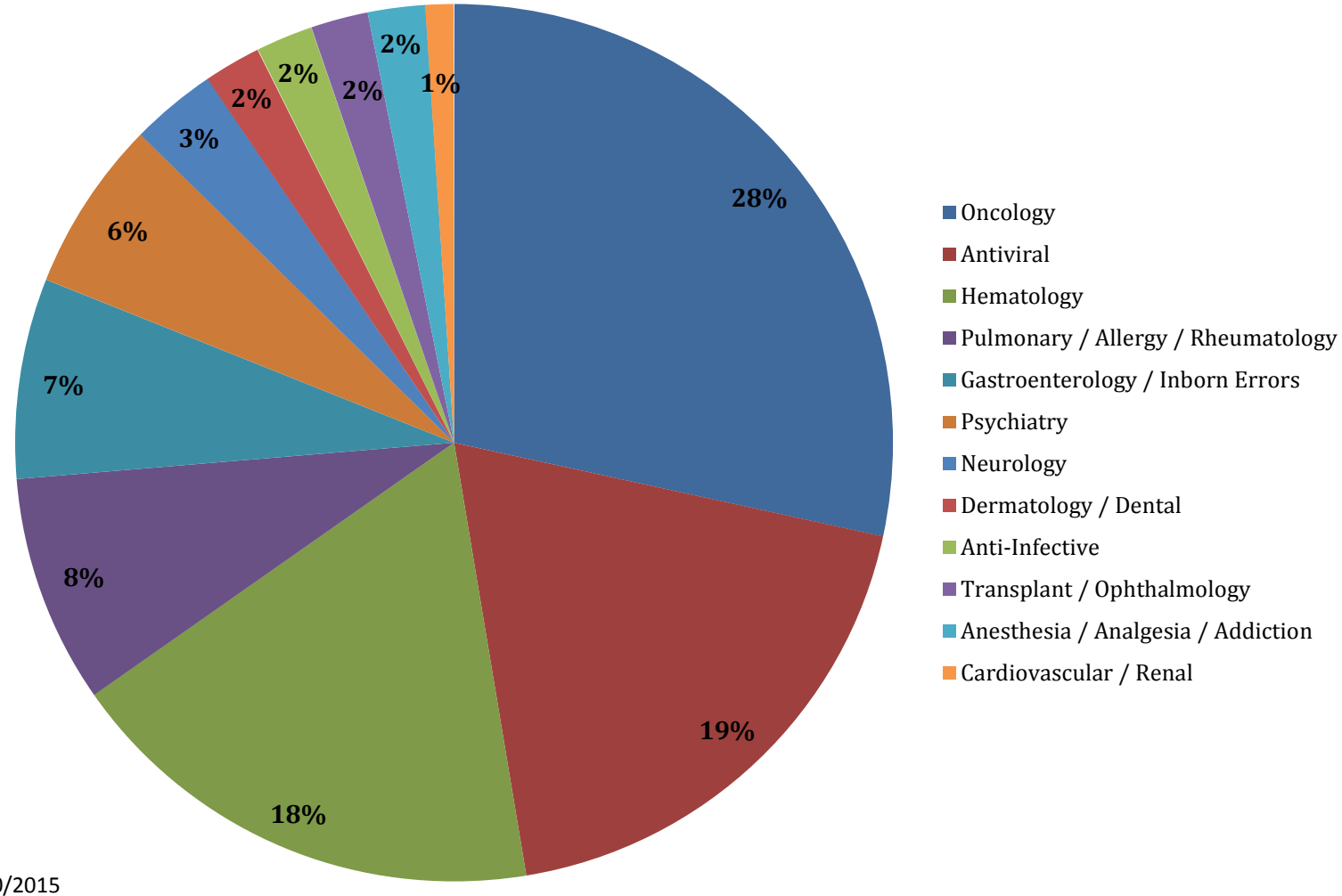
Data as of 11/30/2015

CDER Breakthrough Therapy Requests by Division



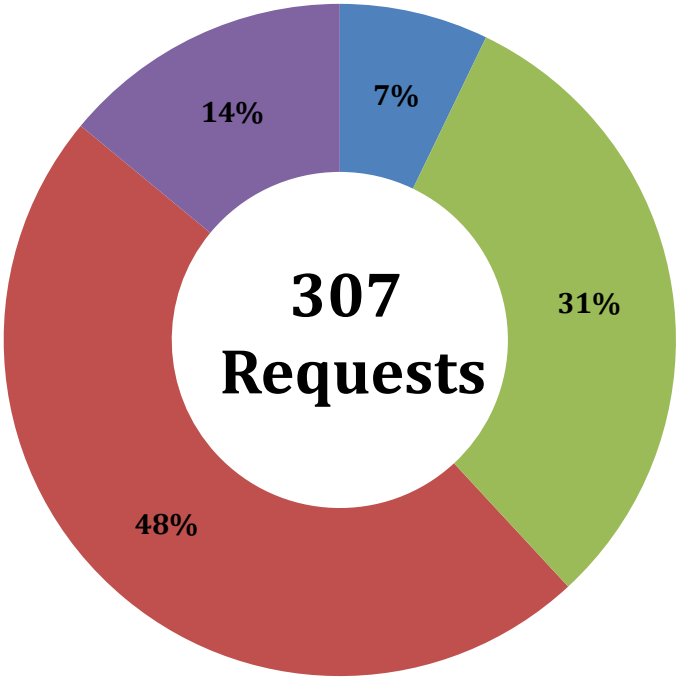
Data as of 11/30/2015

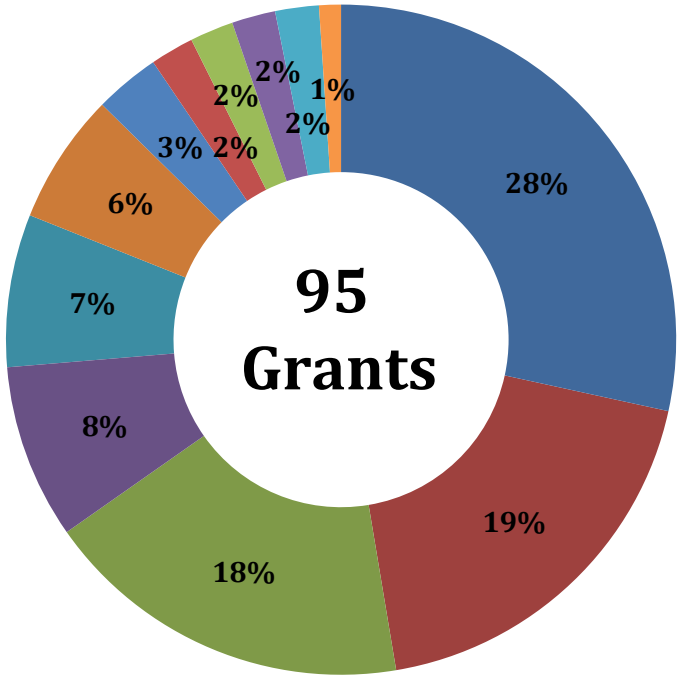
CDER Breakthrough Therapy Requests Granted by Division



Data as of 11/30/2015

CDER Has Granted 95 Breakthrough Therapy Designations Since Inception



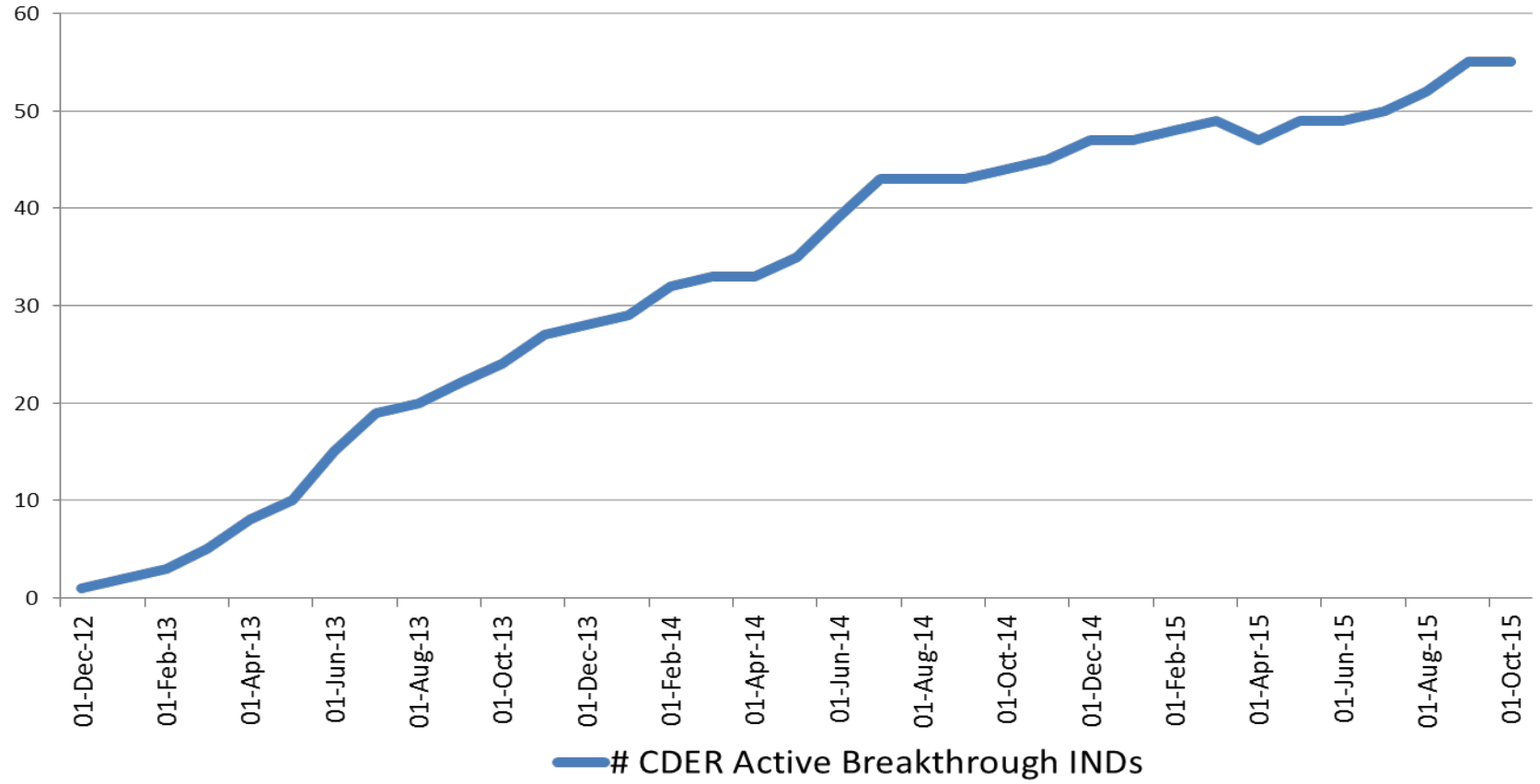


Pending
Granted
Denied
Withdrawn

Oncology
Antiviral
Hematology
Pulmonary / Allergy / Rheumatology
Gastroenterology / Inborn Errors
Psychiatry
Neurology
Dermatology / Dental
Anti-Infective
Transplant / Ophthalmology
Anesthesia / Analgesia / Addiction
Cardiovascular / Renal

Data as of 11/30/2015

Breakthrough Development Program Continues to Grow at a Steady Pace



* Figures includes total # of granted breakthrough designations at the beginning of each month that have yet to have reached either a marketing approval, rescision decision, or discontinued IND development.

Breakthrough Therapies: Three-year Assessment

- "Bar" for designation remains unclear for applicants/public
  - Statutory criteria are subjective, require judgment by FDA
  - BT submission/review under IND impedes clarity/transparency
  - CDER MPC provides consistency for internal decisions
  - Brookings workshop on April 24, 2015, "Breakthrough therapy designation: Exploring the qualifying criteria"
    - http://www.brookings.edu/events/2015/04/24-fda-breakthrough-therapy-criteria
- Pace of requests and % granted for BT designation have remained steady
- Clinical development often NOT the rate-limiting step
  - CMC/GCP deficiencies often delay review completion/approval

Breakthrough Therapies: Three-year Assessment (2)

- Program commitments are very resource intensive for FDA
  - No resources for BT program were provided under PFUFA/FDASIA
  - Growing number of "all-hands on deck" development programs and NDA/BLA/supplement reviews are straining FDA's resources
  - Resource needs must be addressed for continued success
- Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable
    - e.g., small numbers of patients or inadequate duration of follow up
  - Failure to demonstrate "substantial" improvement over available therapy vs "expected" incremental benefit of development programs
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies

Thank You!